IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Michael A. Zeligs	Confirmation No.:	2485
Serial No.:	10/765,792	Art Unit:	1618
Filed:	January 26, 2004	Examiner:	Ebrahim, Nabila G
For:	Phytochemicals for the Treatment of Mastalgia and Endometriosis	Attorney Docket No:	9439-016-999

DECLARATION OF MICHAEL A. ZELIGS UNDER 37 C.F.R. 1.131

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael A. Zeligs, do declare and state that:

1. I am a citizen of the United States residing at 568 Rembrandt Road, Boulder, Colorado 80302.

2. I earned a Master's degree in Physiology, Graduate School of Biology, University of California, Santa Barbara, California, in 1972, and a M.D. from the College of Medicine, University of California, Irvine in 1977. I have completed specialty medical training in Anesthesiology, Pediatrics, and Molecular Immunology. As a physician-investigator, I have studied hormonal influences on health beginning with clinical uses of dehydroepiandrosterone ("DHEA") in the 1980's. In the 1990's, I began to study estrogen-related disorders, including breast disorders, endometriosis, and cervical dysplasia. I am founder of the company BioResponse, LLC.

3. I am the inventor of the invention described and claimed in the above-identified patent application, Serial No. 10/765,792 ("the '792 application"). The invention relates to methods of treating endometriosis in a subject by administering a dietary indole.

4. I have been informed and believe that claims of the '792 application are subject to a rejection based on Liang Jin *et al.*, 1999, Cancer Research 59:3991-3997 (hereinafter "Liang") in view of U.S. Patent No. 6,001,868 (hereinafter "Firestone"), and U.S.

Patent No. 5,981,568 (hereinafter "Kunz") and further in view of Symonds *et al.*, "AGUS in cervical endometriosis," J. Reprod. Med. 1997 Jan; 42(1):39-43 (hereinafter "Symonds").

5. Attached hereto as Exhibit 1 is a copy of U.S. Patent No. 6,689,387 B1. The filing date of this patent is September 23, 1999. I hereby confirm that the acts described in Section 12 of Exhibit 1 were carried out by me or at my direction in the United States of America prior to April 26, 1999.

6. Prior to August 15, 1999, I had treated several patients with known endometriosis with DIM, observing beneficial clinical responses. As shown in Exhibit 1, I treated a 32 year old woman ("P.M.") with endometriosis by administering diindolylmethane ("DIM") (see col. 14, line 30 to col. 15, line 15). P.M., a 32 year old woman, sought alternatives in her management of severe endometriosis. Her symptoms of recurrent midcycle and menstrually associated pain had been diagnosed as due to endometriosis based on pelvic laparoscopy. This procedure confirmed aggressive endometriosis with ectopic endometrial implants removed from the pelvis and associated with intestinal serosal spread. A history of 2 years of intense pelvic pain at mid-cycle and during menstrual flow was reported prior to the laparoscopy. Following the patient's laparoscopy, one menstrual period was still associated with significant, continuing pain. The persisting pain and elevation of serum Ca-125 antigen level (54.1 units/ml) before DIM therapy confirmed ongoing, active endometriosis. Treatment with "processed DIM" was begun approximately 6 weeks following the laparoscopy. The initial dose of 300 mg/day of processed DIM was reduced to 150 mg/day of processed DIM after one month. Since starting treatment, there was disappearance of pain at midcycle and improvement of pain associated with menses. The prolonged reduction of the elevated Ca-125 antigen level during DIM use (26.4, 23.2, and 34.0 units/ml) provided additional, objective evidence supporting the therapeutic response to DIM. The patient continued treatment with processed DIM for about one year. During this time, regular menstrual periods became more comfortable, no longer requiring analgesics. Therefore, the treatment of a patient with endometriosis with processed DIM achieved positive results.

7. Attached hereto as Exhibit 2 is a copy of an April 26, 1999 chart note for "P.M." describing the treatment of P.M. noted above in paragraph 6. This document has been redacted to eliminate the name of the patient. Exhibit 2 shows that by April 26, 1999, patient P.M. had been treated with "Indolplex™" (BioResponse's trademark for its "processed DIM").

Conceptions
Women's Health and Fertility Specialists, P.C.

MAZ

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CHART NOTE:

4-26-99 — [redacted] BD: 9/4/66

Since last seen by Dr. Moore in October, 1998, this 33-year-old nulligravid woman has been relatively free of pelvic discomfort associated with endometriosis treated at laparoscopy by Al Purdon in March, 1998, at which time he performed right salpingo-oophorectomy and vaporization and adhesiolysis of endometriosis. She has not had any hormonal management of the condition thus far, but she has been under the care of Dr. Michael Zeligs, who has administered Indole-Plex with seemingly good results. The reason for consultation today is early recurrence of pelvic discomfort that the patient attributes to endometriosis. Before her surgery in March, 1998, she had an elevated CA-125, in the range of about 70. The value fell to 54 six weeks postoperatively, then 23 in September, 1998, shortly after she began Indole-Plex management. The value in January of this year was 37, and in March it had risen further to 49. Estradiol concentrations in September, 1998 and March, 1999 were 97 and 48 pg/ml respectively.

Today I performed a pelvic examination, finding it to be entirely normal. Likewise, ultrasound examination discloses a normal-appearing left ovary, free of obvious endometriosis, and the remainder of the pelvic findings are likewise normal. A Pap smear was submitted.

At the patient's request, I prescribed Loestrin 1/20-21 to be administered in continuous fashion. I certainly concur with this decision to give estrogen/progestin suppression of ovarian function, both to discourage advancement of endometriosis and perhaps colonization of the remaining ovary, and also in an effort to produce amenorrhea. The patient understands that it may be necessary to experiment with different oral contraceptives preparations to achieve the desired goal. A potential complicating feature is that she plans to leave the Boulder area for Pennsylvania in four weeks, where she will begin a program to become a physician's assistant. I told her that we could troubleshoot the regimen, if necessary, by either phone or fax. She will be back in this area in August. I gave her a prescription for Loestrin refillable until approximately that time.
Richard J. Worley, M.D./cb
cc: Dr. Michael Zeligs

Exhibit 2

8. Therefore, well before the publication date of Liang, *i.e.*, before August 15, 1999, I had treated a patient having endometriosis with a dietary indole, DIM, and showed that the patient's endometriosis symptoms and Ca-125 antigen level had been significantly reduced.

9. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Sept 20, 2007 Michael A. Zeligs, M.D.